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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,389	11/10/2003	Narayanan Sundararajan	070702009320	4354

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,389	SUNDARARAJAN ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006 and 14 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-20 and 22-45* is/are pending in the application.

4a) Of the above claim(s) *24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 24-45 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 18 April 2006.

Specification

2. The specification contains numerous bibliographic citations, yet it has not been found to contain any statement that the cited documents have been incorporated by reference. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Attention is also directed to MPEP 608.01(p)I, which, in pertinent part, is reproduced below:

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found. (Emphasis added)

3. Accordingly, the cited documents are not considered to have been incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4-20, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94

> (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations; and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary,

The quantity of experimentation necessary for enabling the full s cope of the invention is vast, on the order of several man-years with little if any reasonable expectation of success. As presently worded, the claimed method fairly encompasses the simultaneous sequencing of any number and combination of nucleic acids, including intact chromosomes, ye the disclosure does not set forth a reproducible procedure whereby any nucleic acid could be sequenced, much less reproducibly sequence any intact chromosome.

The amount of direction or guidance presented,

The amount of guidance provided is limited to prophetic showings of how the invention may be practiced.

The presence or absence of working examples,

A review of the disclosure finds the following examples:

a. Example 1, page 23;

b. Example 2, pages 23-24;

c. Example 3, "method for preparing DNA to make RNA," pages 24-34;

d. Example 4, "an exemplary method for covering a surface with a template such as covering a cantilever with an oligonucleotide template," pages 34-36; and

e. Example 5, Raman spectra of deoxyadenosine triphosphate (dATP) solution before and after incorporation, pages 26-37.

A review of the disclosure, including the five examples, fails to find the disclosure of a reproducible procedure whereby the complete nucleotide sequence of any "nucleic acid" can be achieved. As seen above, the nucleic acid can be DNA, RNA, single stranded, double-stranded, or even triplex structures, and that the length of any or all of the nucleic acids can range up to complete chromosomes. The disclosure, however, does not show in such full, clear, concise and exact language how even a 10mer of a single stranded nucleic acid has been accurately and reproducibly sequenced.

Agreement is reached in that there is no *per se* rule that an applicant must provide examples, however, an applicant is still, none the less, required to fully enable the claims' scope, and to also provide such full, clear, concise and exact description of the invention so as to reasonably suggest that applicant had possession of the invention at the time of filing. Such a disclosure has not been found in the instant application.

As noted above, the disclosure contains numerous references to published documents, however, the documents have not been properly incorporated by reference and as such, cannot be relied upon for satisfaction of the written description requirement of 35 USC 112, first paragraph.

The nature of the invention,

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The state of the prior art, and the predictability or unpredictability of the art

The state of the prior art has advanced to where certain problems are known to occur. In support of this position, attention is directed to US Patent 7,129,340 B1, column 18, seventh paragraph, teaches that specificity issues result when using primers greater than 100 nucleotides in length, yet the claimed method fairly encompasses using primers of virtually any length.

The claimed method fairly encompasses the use of virtually any polymerase, including Klenow fragment. US Patent 7,066,453 B2, teaches at column 2:

> The Klenow fragment has several limitations when used for enzymatic sequencing. One limitations is the low processivity of the enzyme, which generates a high background of fragments that terminate by the random dissociation of the enzyme from the template rather

than by the desired termination due to incorporation of a ddNTP. The low processivity also means that the enzyme cannot be used to sequence nucleotides that appear more than 250 nucleotides from the 5' end of the primer. A second limitation is that Klenow cannot efficiently utilize templates which have homopolymer tracts or regions of high secondary structure.

The instant disclosure is silent as to how the issue of premature termination is to be overcome when the target nucleic acid can be of virtually any length, and especially a length of more than 250 nucleotides (see applicants definition of "nucleic acid", *infra*). And the specification is silent as to how the issue of unwanted secondary structures is to be overcome when, as noted in the definition, the nucleic acid can well take on tertiary structures, not just secondary structures, as is the case with chromosomes.

The claimed method fairly encompasses the incorporation of modified nucleotides. US Patent 7,057,026 B2, column 1, teach that the "nucleotide triphosphates modified with a 3'-O-blocking group that is photolabile and fluorescent. The modified nucleotides are intended for use in DNA sequencing experiments. However, these nucleotides proved to be difficult to incorporate onto an existing polynucleotide, due to an inability to fit into the polymerase enzyme active site." Therefore, with the claimed method being dependent upon the monitoring of the very incorporation of nucleotides by a polymerase, which can be modified nucleotides, the method would not function, and the specification is silent as to how such issues of operability could be overcome.

The breadth of the claims.

2. The claims encompass the sequencing of any nucleic acid, no matter how long or complex. In support of this position, attention is directed to the definition of "nucleic acid" as found at page 5 of the specification.

> [0020] "Nucleic acid" 214 encompasses DNA, RNA, single-stranded, double-stranded or triple stranded and any chemical modifications thereof. In certain embodiments of the invention single-stranded nucleic acids 214 may be used. Virtually any modification of the nucleic acid 214 is contemplated. A "nucleic acid" 214 may be of almost any length, from 10, 20, 50, 100, 200, 300, 500, 750, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 6000, 7000, 8000, 9000, 10,000, 15,000, 20,000, 30,000, 40,000, 50,000, 75,000, 100,000, 150,000, 200,000, 500,000, 1,000,000, 2,000,000, 5,000,000 or even more bases in length, up to a full-length chromosomal DNA molecule.

Further, the claims fairly encompasses the use of any polymerase as well as modified nucleotides, all of which are recognized in the art as causing sequencing methods to be inoperative, yet the specification is silent as to how these art-recognized issues are to be overcome.

In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 4-20, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,280,939 B1 (Allen) in view of US Patent 5,807,758 (Lee et al.) and US Patent 6,436,647 B1 (Quate et al.).

10. Allen discloses a method of sequencing nucleic acids where an atomic force microscope cantilever is used. While the movements and mass attributes of the polymerase are detected via the cantilever, the template nucleic acid is not attached to the cantilever.

11. Lee et al., disclose a method of characterizing a nucleic acid wherein the nucleic acid is attached to the surface of a cantilever. As set forth in column 3, one is able to detect whether a

binding member has associated with the immobilized molecule, which is on the surface of the cantilever.

12. Quate et al., teach in greater detail of the binding of molecules to the surface of a cantilever and the detection of molecular interactions.

13. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the aspect of sequencing a nucleic acid as disclosed by Allen where the template nucleic acid is attached to the surface of a cantilever, and the identity of the various nucleotides that are incorporated into the nascent strand are identified by changes in the stress property of the cantilever.

14. In view of the detailed teachings of the prior art, the ordinary artisan would have had a most reasonable expectation of success, and would have been amply motivated as the method would achieve the same result, sequencing of a nucleic acid, but do so in a more direct manner by having the molecules of interest being attached to the cantilever, and therein requiring less steps and manipulation.

15. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1, 4-20, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,280,939 B1 (Allen) in view of US Patent 5,807,758 (Lee et al.) and US Patent 6,436,647 B1 (Quate et al.).

Conclusion

16. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

18. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS